REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 43-50 are currently pending and under examination in the application. Without acquiescence or prejudice, claim 43 is amended to particularly point out and distinctly claim certain embodiments of Applicants' invention. No new matter has been added by the amendment. Support for the amendment can be found in the specifically as originally filed, for example, at page 18, lines 15-17; and page 27, lines 29-30. *See also* M.P.E.P. § 2173.05(i), citing *In re Johnson*, 558 F.2d 1008, 1019 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."), for the principle that if alternative elements are positively recited in the specification, then they may be explicitly excluded in the claims.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 43-45 and 48 stand rejected under 35 U.S.C. § 102(e) for alleged lack of novelty over Klose *et al.* (U.S. Patent No. 6,916,486). The Examiner asserts that Klose *et al.* teach an analgesic compound for treatment of neuropathic pain comprising flupirtine and other opioid analgesics. Essentially, the Examiner asserts that the presently claimed combination of flupirtine and other recited opioids is anticipated by claims 11 and 12 of Klose *et al.*, which allegedly recite administering at least one analgesic selected from a list that includes opioids and flupirtine.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of novelty in view of Klose *et al.* Embodiments of the instant claims relate, in pertinent part, to methods for inducing an analgesic response to neuropathic pain, comprising administering flupirtine in combination with a recited opioid, excluding topical administration.

Klose *et al.* fail to disclose each feature of the instant claims. Mainly, this reference is at best limited to transdermal (*i.e.,* topical) administration of the formulations described therein, a route that is excluded by the instant claims. Klose *et al.* do not contemplate any other forms of administration, such as oral, subcutaneous, intramuscular, intravenous, intrasternal, intrathecal, and epidural administration, among others (*see, e.g.,* page 18, lines 17-

21 of the instant specification), but instead focus entirely on transdermal administration (*see, e.g.,* column 3, lines 15-20; and column 4, lines 57-62 of Klose *et al.*). By being limited to transdermal administration, Klose *et al.* fail to anticipate the instant claims.

Applicants, therefore, submit that the instant claims satisfy the requirements of novelty over Klose *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

REJECTIONS UNDER 35 U.S.C. § 103

A. Claim 47 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Klose *et al.* in view of Devulder *et al.* The Examiner agrees that Klose *et al.* fail to teach the dosage range recited in claim 47, but asserts that Devulder *et al.* teach a flupirtine dosage range that fails within the claimed range. The Examiner, thus, asserts that the it would have been obvious to utilize the dosage range of Devulder *et al.* in the method of Klose *et al.*

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Klose *et al.* in view of Perovic *et al.* The Examiner agrees that Klose *et al.* fail to disclose the absence of overt sedation of opioids in the presence of flupirtine. The Examiner asserts, however, that Perovic *et al.* teach that flupirtine rarely causes drowsiness, and further asserts that since the claims encompass an almost negligible amount of opioid, such overt sedation would obviously not occur since it is dose related.

C. Claims 49 and 50 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Williams *et al.* (U.S. Application No. 2003/82214) and Cleary *et al.* (*Cancer Control*. 7:120-131, 2000). The Examiner asserts that Williams *et al.* teach compositions of flupirtine and an opioid for treating cancer-associated neuropathic pain, but agrees that they do not teach the specific cancers of claim 50. The Examiner, however, asserts that Cleary *et al.* not only teach that cancer has a neuropathic component, but identifies such cancers, including colon cancer and non-small cell lung cancer.

Applicants traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over any combination of the above-cited references, because the Examiner has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d

1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). In this regard, the cited references not only fail to teach or suggest all of the claim features, but fail to provide any apparent reason to practice the presently claimed methods with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Mainly, the cited references fail to teach or suggest the step of administering flupirtine in combination with an opioid in an amount effective to reduce the level of or to otherwise ameliorate the sensation of pain, excluding topical administration.

As to the rejections in sections A and B above, the cited references in combination fail to teach or suggest each feature of the instant claims. For instance, Klose *et al.* are at best limited to transdermal administration of the formulations described therein, a route that is excluded by the instant claims. Klose *et al.* do not contemplate any other forms of administration, such as oral, subcutaneous, intramuscular, intravenous, intrasternal, intrathecal, epidural and intradermal administration (*see, e.g.,* page 18, lines 17-21 of the instant specification), but instead focus entirely on transdermal administration (*see, e.g.,* column 3, lines 15-20; and column 4, lines 57-62 of Klose *et al.*). This deficiency in Klose *et al.* is not remedied by either Devulder *et al.* or Perovic *et al.*, because neither of these references teach or suggest the administration of flupirtine in combination with an opioid, excluding topical administration. By failing to teach or suggest each feature of claims 46 and 47, Klose *et al.*, in combination with either Devulder *et al.* or Perovic *et al.*, fail to provide a requisite element of a *prima facie* case of obviousness with respect to these claims.

The combination of these references also fails to provide a reasonable expectation of success in practicing the instant methods. As noted above, Klose *et al.* are limited to transdermal administration. In contrast to this reference, the instant claims exclude topical administration such as transdermal administration. Hence, even if persons skilled in the art at the time of invention combined Klose *et al.* with either Devulder *et al.* or Perovic *et al.*, they would not have arrived at the presently claimed methods at all, let alone with a reasonable expectation of success. Instead, to practice the instant claims from Klose *et al.*, in combination with either

Devulder *et al.* or Perovic *et al.*, persons skilled in the art would have had to embark on a whole new line of experimentation, such as that performed by Applicants, to arrive at the understanding that flupirtine in combination with the recited opioids provides unexpected synergistic effect in treating the particular problems associated with neuropathic pain, especially for non-topical applications (*see, e.g.,* page 45, lines 4-16 of the specification). Given the limited amount of tangible, technical information in these references, the suggestion for such a new line of experimentation cannot be found in any of Klose *et al.*, Devulder *et al.*, or Perovic *et al.*, nor can a reasonable expectation that such a line of experimentation would have been successful.

To the contrary, as shown in the Declaration of Michael Stephen Roberts, Ph.D (the "Roberts Declaration"), the methods of Klose *et al.* are inadequate to practice the instant methods, in part because they fail to provide adequate blood levels of flupirtine to have any significant effect on neuropathic pain (*see, e.g.,* Items 7-12 of the Roberts Declaration). In this regard, the Roberts Declaration discusses the maximum dose of flupirtine that can be absorbed across the skin (*i.e.,* transdermally) over a 24 hour period. Specifically, even when using a large 800 cm^2 patch, the amount absorbed over 24 hours would be in the order of 2.4mg, an amount that is less than 1/100th of the lowest flupirtine dose required for ***effective*** pharmacological activity (*see* paragraph 12 of the Roberts Declaration), as presently claimed. Thus, especially outside of transdermal applications, the limited teachings of the methods of Klose *et al.*, even in combination with Devulder *et al.* or Perovic *et al.*, fail to provide any expectation that flupirtine could have been administered in combination with an opioid to effectively reduce the level of or to otherwise ameliorate the sensation of pain reduce neuropathic pain. By failing to provide an apparent reason to practice the subject matter of the instant claims with a reasonable expectation of success, Klose *et al.*, in combination with either Devulder *et al.* or Perovic *et al.*, fail to establish a *prima facie* case of obviousness over these claims.

As to the rejection in section C above, the cited references in combination fail to teach or suggest each feature of the instant claims. For example, similar to Klose *et al.*, Williams *et al.* are at best limited to topical administration of the formulations described therein, a route that is excluded by the instant claims. This deficiency in Williams *et al.* is not remedied by Cleary *et al.*, because this reference also fails to teach or suggest the administration of flupirtine

in combination with an opioid, excluding topical administration. By failing in combination to teach or suggest each feature of claims 49 and 50, Williams *et al.* and Cleary *et al.* fail to provide a requisite element of a *prima facie* case of obviousness with respect to these claims.

Further, the combination of Williams *et al.* and Cleary *et al.* fails to provide a reasonable expectation of success in practicing the instant methods. Mainly, Williams *et al.* are not only limited to topical or intradermal administration, but teach that their methods are to avoid transfer of the pharmaceutical into the blood stream (*see, e.g.,* paragraphs [0046] and [0047] of Williams *et al.*). Indeed, Williams *et al.* teach that their topical-based methods allow the use of compounds that are otherwise unsuitable for systemic use (*see, e.g.,* paragraph [0063] of Williams *et al.*). The generic discussion in Cleary *et al.* does not remedy this deficiency in Williams *et al.*, especially with regard to the specific combination of flupirtine and an opioid. In contrast to these references, the instant claims exclude topical administration. Hence, even if persons skilled in the art at the time of invention combined Williams *et al.* Cleary *et al.*, they would not have arrived at the presently claimed methods at all, let alone with a reasonable expectation of success.

Moreover, Williams *et al.*, essentially "teach away" from the instant methods, which are based in part on non-topical routes of administration that necessarily transfer the pharmaceuticals into the blood stream. *See, e.g.,* M.P.E.P. § 1504.03(III), citing *In re Haruna*, 249 F.3d 1327 (Fed. Cir. 2001) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference…would be led in a direction divergent that was taken by the applicant."). Specifically, Williams *et al.*, at best, would have led persons skilled in the art in a direction divergent than that of the instant claims, towards methods of administration that avoid or limit transfer of the instant compositions into the blood stream, and away from the instant non-topical methods of administration. Overall, by failing to provide an apparent reason to practice the methods of claims 49 and 50 with a reasonable expectation of success, and by essentially teaching away from such methods, the combination of Williams *et al.* and Cleary *et al.* fails to establish a *prima facie* case of obviousness over these claims.

As to each of the rejections in sections A, B, and C above, and as previously made of record, Applicants emphasize that the non-obviousness of the instant claims is supported by

secondary considerations, such as improved properties and unexpected results. *See, e.g., In re Dillon,* 919 F.2d 688, 692, 693 (Fed. Cir. 1990). In this regard, it is respectfully submitted that ***synergism*** may point toward non-obviousness. *See* M.P.E.P. § 2141(I). Here, as noted above, it was unexpected to find that the combination of flupirtine and an opioid ***synergistically*** reduces pain symptoms (*see, e.g.,* page 45, lines 4-16 of the specification), thereby allowing the use of reduced levels of opioids during neuropathic pain therapy. This unexpected benefit alone is therapeutically significant in the treatment of neuropathic pain, because the use of opioids is often frequent and sustained due to the diminished effects of opioids in subjects suffering from neuropathic pain. Such over use is often associated with addiction, the development of tolerance, and an increase in the number and severity of side effects associated with opioid use (*see, e.g.,* page 4, lines 8-11 of the instant specification). Among other benefits, these ***synergistic effects*** allow those undergoing neuropathic pain management therapy to reduce the risk of tolerance, avoid the life-interfering effects of overt sedation (*see, e.g.,* page 14, lines 23-29 of the instant specification), as well as manage other side effects, including euphoric effects, emetic effects, spastic constipation and increased smooth muscle tone (*see, e.g.,* page 4, lines 11-12 of the instant specification). Therefore, the unexpected ***synergistic results*** demonstrated by Applicants provide real-world benefits in neuropathic pain therapy, and clearly support the non-obviousness of the instant claims.

In view of the remarks and amendments provided herein, Applicants submit that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. However, should the Examiner believe that the claims are not in condition for allowance, she is respectfully requested to telephone the undersigned to resolve any outstanding issues. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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